ROR2: Novel target for the promotion of healthy cartilage in osteoarthritis

Novel experimental treatment shows promise in eliminating pain and reversing structural changes in murine models of osteoarthritis. These unique therapies target ROR2, a non-redundant marker expressed minimally in adult tissues, potentially becoming groundbreaking disease-modifying treatments for osteoarthritis.

Background

Osteoarthritis (OA) is a debilitating joint disease characterised by breakdown of the articular cartilage and bone changes, including thickening of the bone supporting the cartilage and excessive bone formation at the margins of the joint (osteophytes).

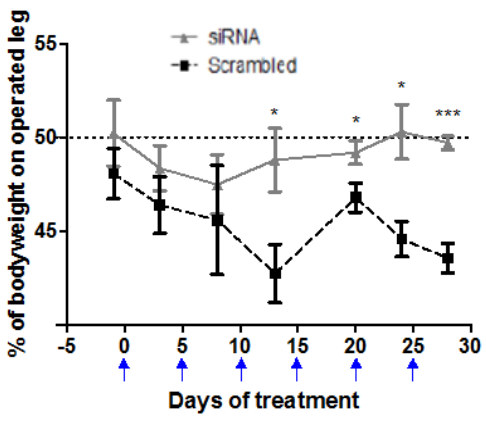
The Problem

There are no disease modifying therapies to treat the cause of osteoarthritis. Current treatment consists of symptom management with non-steroidal anti-inflammatory drugs, eventually joint replacement. Hence, there is an urgent unmet need for a new therapeutic approach targeting and resolving the etiology of the disease.

Invention: Benefits & Application

The therapy's success hinges on their unique approach, leveraging a novel cell-surface receptor that is specifically upregulated in cartilage due to local inflammation and mechanical stress, while maintaining minimal expression in physiological conditions. The blockage of this receptor, using nucleic acids and proteins, has been shown to initiate a cascade of events leading to cartilage repair and sustained pain relief, as depicted in Figures 1A and 2B. This restorative process involves two key mechanisms: the prevention of cartilage degradation and the induction of cartilage formation.

A



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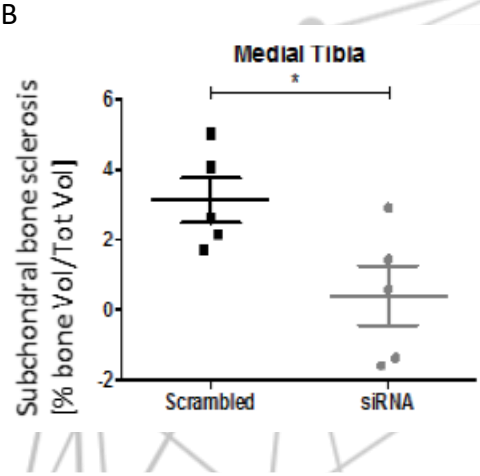

Fig. 1. siRNA-silencing treatment of skeletally mature mice with surgically-induced menisco- ligament injury (MLI) to one hind limb resulted in significantly reduced pain on weight bearing as compared to control mice **(A)** and prevention of pathological growth of the medial tibia **(B)**

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siRNA silencing of the target receptor *in vivo* reduces cartilage breakdown in the meniscal/ligamentous injury model of OA. To prevent cartilage degradation, blocking ROR2 with nucleic acids and proteins inhibits the expression of crucial cartilage-degrading enzymes, specifically ADAMTS-4 and -5, resulting in a significant reduction in cartilage breakdown observed *in vivo*, as illustrated in Figure 2A. Simultaneously, the novel therapies induce cartilage formation by facilitating *in vitro* chondrogenic differentiation of mesenchymal stem cells. These interventions also curb the pathological growth of the medial tibia, as shown in Figure 1B.

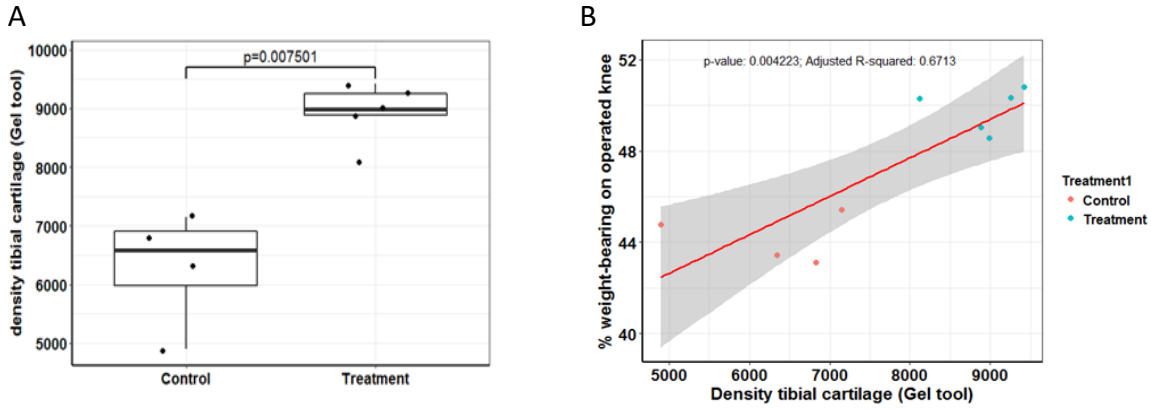

Fig 2. Degradation of glycosaminoglycans (GAGs) contribute to the reduction of tibial cartilage, considered an early feature in developing OA. (A) A significant reduction in degradation of GAGs was observed in skeletally mature mice injected with siRNA inhibiting the target receptor. (B) Correlation between density of the cartilage and percentage of body weight carried on the limb with meniscal/ligamentous injury: The extent of cartilage breakdown correlates with pain.

Blocking ROR2 additionally contributes to an increase in the size and differentiation of human cartilage organoids, as evidenced in Figure 3. These combined mechanisms of preventing degradation and promoting cartilage formation underpin the therapy's effectiveness in alleviating pain and repairing damaged cartilage.

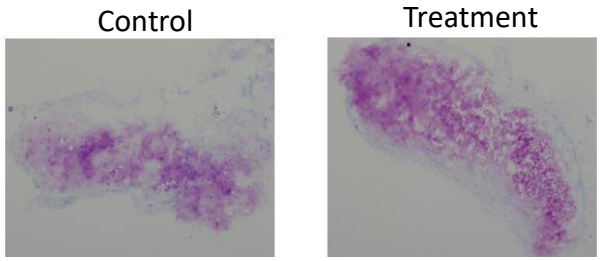

Fig 3. Human articular chondrocytes form cartilage organoids when implanted ectopically in nude mice. RNA-silencing of the target receptor resulted in significantly increased GAG content in human cartilage organoids.

Lead Inventor

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Patent

A patent application, WO/2019/097247, has been granted in several jurisdictions including: US, CN, GB, DE, AT, BE, CH, FR, IE, NL.

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